Amendments to the Drawings:

Please replace Figure 1 illustration by following content:

> Figure 1 is X-ray powder diffraction pattern of [[novel]] amorphous form of memantine hydrochloride.

Please discard Figure 2.

REMARKS/ARGUMENTS

In the specification, the paragraph on page 1 (lines 7-9) has been amended to correct minor editorial problems. The chemical structure is included in page 1. The new paragraph added after last paragraph on page 2 (or at the beginning of the page 3) summarizes in general terms the needs and benefits of the current invention.

Figure 2 is the chemical structure of memantine hydrochloride. Since this chemical structure is placed in the amended paragraph on page 1 (lines 7-9), Figure 2 is no longer needed.

Claims1-2 have been amended in this application. Claim 19 is cancelled. Claims 3-18 remain in this application.

In view of the examiner's restriction requirements or rejections, applicant retains the right to present claims 1-18. Applicant presents following remarks or arguments.

For claim1, after deleting the word "novel", this claim now has a particular and distinct subject matter, which is the amorphous form of a compound (memnatine hydrochloride). The subject matter in this claim is the crystal modifications of a compound (drug substance), not two sets of compounds. Two sets of compounds mean two chemical identities, which include different chemical structures and/or structural isomers such as regio-isomers or stereoisomers. Therefore, the amended claim 1 covers the crystal modification such as non-crystalline or amorphous form of the same molecule, and such claim is proper under 35 USC112.

For claim 2, after amended, the featureless (lack of any discernible peaks) X-ray powder diffraction pattern in this claim now is, clearly and only, for amorphous form of

memantine hydrochloride, not for any non-crystalline sample of any compound. Additionally, the applicant also amended the claim so that no Figure 1 is referenced in the claim. Therefore, the amended claim 2 is also allowable under 35 USC112.

The remaining claims 3-16 are also proper under 35 USC112 since amended claims 1 and 2 have definite claims and are proper.

As for examiner's view on claim 1-19 rejections based on 35 USC 103(a) obviousness due to a prior art, *Polymorphism in Molecular Crystals* by Joel Berstein, Oxford University Press Inc., New York (2002) pages 253-254 and further in view of US5,614,560, cited by applicant in the IDS, the applicant like to present following remarks and arguments.

Firstly, the prior art (*Polymorphism in Molecular Crystals* described above) is just a general reference teaching some general knowledge on the crystal modifications of organic molecules, with only one and half page (pages 253-254) describing amorphous form in very general terms. On page 254, it is stated that amorphous forms are typically prepared by employing crystallization procedures far from equilibrium such as, for instance: rapid solidification from the melt, lyophillization, spray drying, solvent removal, precipitation by pH change, or by various mechanic processes.

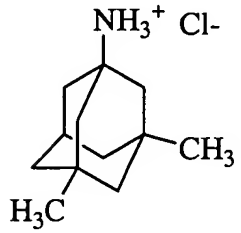
The prior art only provides general technical terminologies of how amorphous form of any materials might be produced, as many other prior arts already did so. The prior art does not provide any specific procedures or conditions to produce amorphous form of any or a particular pharmaceutical compound. There are fundamental differences between the terminologies and procedures: procedures are processes and terminologies are just concepts of technologies. The prior art does not give any information which solvent(s) to dissolve the material(s), what concentration is required, what temperature to heat or cool the solution(s), which technology should be used to obtain the desirable non-crystalline or amorphous form for a particular compound. The ordinary skill in the art can

not produce desirable amorphous form (e.g., pure amorphous form) of memantine hydrochloride by following the prior art cited by examiner.

For instance, applicant found that rapid solidification from the melt of memantine hydrochloride did not give its amorphous form. Instead, this process resulted in the loss of potency of memantine hydrochloride with over 30% due to degradation or decompositions. Precipitation by pH change did not produce any amorphous form of memantine hydrochloride at all. Various mechanic processes such as milling or grounding also did not produce the desirable amorphous form (more than 20% crystal form exists). Lyophillization and solvent removal also failed to produce desirable amorphous form of memantine hydrochloride in applicant's initial attempts.

This is because memantine hydrochloride has novel or unique physiochemical properties. For example, its crystal habit, solubility, crystal energy, crystal packing and crystal formation kinetic and dynamic processes are totally different from other molecules. The amorphous form of memantine hydrochloride can be obtained only under certain optimized conditions through experimental studies using relevant processes and applicable conditions. There are so many factors such as properties of solutes, solvent nature, solution temperature, solution concentration, pressure and solvent-removing technology (e.g., type and speed etc) contributing the outcome of the production of mamentine hydrochloride amorphous. In conclusion, ordinary skill in the art is not able to obtain amorphous form of memantine hydrochloride by using reference titled as *Polymorphism in Molecular Crystals* described above.

Secondly, but more importantly, in this application, memantine hydrochloride is a unique pharmaceutical molecule (compound) and it has a very unusually high melting point [290-295°C, according to Journal of Medicinal Chemistry" 6(1963), p763]. All other adamantine derivatives also have very unusually high melting points. For example, rimantadine hydrochloride has a melting point of 373-375 °C (see Merck Index, 12th edition, p.1642, #8390). This class of organic salts contains a large cyclic and hydrophobic adamantine group and a hydrophilic protonated amine group, as shown below:



They have a very strong tendency to readily form highly organized crystals with huge crystal lattice energy, leading to high melting points. The novel structure and property would renders these types of compounds particularly easy to crystallize in solutions or in solid states, but very difficult and challenge for formation or production of its amorphous form, particularly pure amorphous form which is useful in pharmaceutical industry, by ordinary skill in the art, or even by experts in the art. This is because the crystal form is thermodynamically much more stable the corresponding amorphous (usually regarded as metastable) form, particularly when a large energy differences between the crystal form and amorphous form exists, which would make the amorphous form even less table, and thus much more difficult to make. That is why no amorphous form of memantine hydrochloride has not been obtained and reported yet even this compound has been known over four decades, and only its crystalline forms have been obtained and reported so far. However, the amorphous form of memantine hydrochloride may have much better solubility, dissolution and bioavailability than the corresponding crystal forms. The large crystal lattice energy and high melting points of crystal forms make its solubility, dissolution and bioavailability undesirable.

Therefore, there is along-felt need in the industry for amorphous form of memantine hydrochloride, and it is desirable to have a procedure that can make its pure amorphous form (e.g., containing less than 10% crystal forms). Due to its novel properties, the production of amouphous form, particularly pure amorphous form of memantine hydrochloride, requires novel processes and conditions which are not obvious to the ordinary skill in the art. Therefore, both amorphous form and its production processes are not obvious, and consistent with the requirements of unobviousness as defined in 35 USC, 103 (a). Such amorphous form cannot be obtained by the ordinary skill in the pertinent arts or by using the prior art cited by examiner. In other words, the

scope and contents in the prior art (*Polymorphism in Molecular Crystals* described above) do not teach the subject matter of this invention, and there are ascertained differences between the prior art and the subject matter of this invention, as further explained below.

The applicant found that ordinary skill in the art can not obtain the amorphous form of memantine hydrochloride by following the prior art cited by examiner or other prior arts. For example, the applicant found that the desirable non-crystalline or amorphous form of memantine hydrochloride can not be produced by precipitation by pH change, rapid solidification from the melt, or by converting crystals into amorphous form through various mechanic processes such as milling or grounding, or even by distilling solvent(s) under certain conditions, as suggested in the reference titled as *Polymorphism in Molecular Crystals* described above. Even by lyophillization process, it was found to give crystal form of memantine hydrochloride under certain conditions. A reference (WO2005/069742, priority data:1258/MUM/2003, example 2) also indicated that they obtained crystal form II through distilling solvent under certain conditions. That is, the applicant found that many technologies used to generate amorphous forms are not applicable or useful to the production of amorphous form of memantine hydrochloride. Only novel, unique or special procedures or processes detailed in the applicant's patent application can lead to the production of desirable amorphous form of memantine hydrochloride (less than 10% crystal forms). In order to prevent the conversion of amorphous form into crystal forms, the pure amorphous form (or less than 10% crystal form) is preferred. This is particularly true for memantine hydrochloride since its crystal forms have huge stability advantage.

Therefore, amorphous form of memantine hydrochloride, and its processes of making have not been obvious to the ordinary skill in the art at the time of the invention. The differences between the prior art and the claims at issue ascertains the novelty and unobviousness of this invention. The scope and contents of the prior art do not teach the subject matter of this invention.

In summary, the subject matter of this invention is novel and unobvious to ordinary skill in the art and thus Claims 1-16 are proper according to the patent law, 35 USC, 103(a).

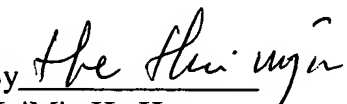
Amorphous form of memantine hydrochloride is a new, previously unprepared or uncharacterized form of this compound. It is also a useful pharmaceutical agent and can be used to make pharmaceutical dosage forms. Therefore, Claims 17-18 to use it in pharmaceutical compositions such as dosage forms is proper. There are many pertinent cases in US patents (see recent patents granted to amorphous forms of a particular pharmaceutical compound and their production processes: US6696458 and US6894066).

The patentability standard should be the same throughout the Office (manual of Patent Examination Procedure, Rev. 2, 2004, 700-18).

Reference US5,614,560 is the basic patent covering the method of use of compound itself or its salts, not covering the polymorph forms (including amorphous form) of such compounds. Case law cited by examiner covers patent cases regarding the different molecule entity (isomeric compound, different compound or different chemical structure), and thus it is not applicable to the patentability of polymorph forms-including amorphous form- of the same compound (or same chemical entity).

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
MaiDe Ltd.

By 
HuiMin He-Huang

Tel: (508)393-4406

Statement of no new matter added in substitute specifications

Sir:

In response to the Office action of June 13, 2005 and Interview dated August 08, 2005, please see amended substitute specifications (both marked up version and clean version are submitted). There is no new matter added in the substitute specifications.

Respectfully submitted,
MaiDe Ltd.

By He Huimin
HuiMin He-Huang
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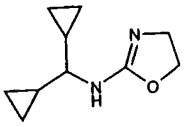
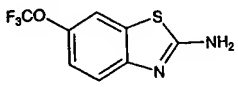
Monohydrochloride dihydrate, $C_{21}H_{20}Cl_2N_6O_3.HCl.2H_2O$, *450191-S, Rhythmy.* Solid from 95% ethanol, mp 107°. LD_{50} orally in mice: >1500 mg/kg (Hirai, 1979).
THERAP CAT: Sedative, hypnotic.

8388. Rilmenidine. *N-(Dicyclopropylmethyl)-4,5-dihydro-2-oxazolamine;* 2-[*N*-(dicyclopropylmethyl)amino]-oxazoline; oxaminozoline; S-3341. $C_{10}H_{16}N_2O$; mol wt 180.25. C 66.64%, H 8.95%, N 15.54%, O 8.88%. α_2-Adrenoceptor agonist. Prepn: C. Malen *et al.*, Ger. pat. 2,362,754; *eidem*, U.S. pat. 4,102,890 (1974, 1978 both to Sci. Union et Cie. - Soc. Franc. Recher. Med.). Adrenoceptor binding study: P. Guicheney *et al.*, *J. Pharmacol.* **12**, 255 (1981). Pharmacokinetics in hypertensive subjects: J. Velly *et al.*, *ibid.* **13**, 413 (1982). Animal pharmacology: M. Laubie *et al.*, *ibid.* **16**, 259 (1985); P. A. van Zwieten *et al.*, *Arch. Int. Pharmacodyn.* **279**, 130 (1986). Hypotensive effect in humans: K. Weerasuriya *et al.*, *Eur. J. Clin. Pharmacol.* **27**, 281 (1984). Mechanism of action study: R. E. Gomez *et al.*, *Eur. J. Pharmacol.* **195**, 181 (1991). *Review:* T. J. Verbeuren *et al.*, *Cardiovasc. Drug Rev.* **8**, 56-70 (1990).



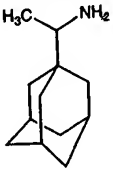
Crystals from hexane, mp 106-107°.
Phosphate, $C_{10}H_{16}N_2O.H_3PO_4$, *S-3341-3, Hyperium.* pKa 9.3. Soly in H_2O: ~19% w/v; in methanol: ~7% w/v; in chloroform and ethanol: ~0.7% w/v. LD_{50} orally in mice, rats: 375, 295 mg/kg (Verbeuren).
Fumarate, $C_{14}H_{20}N_2O_5$, crystals from ethanol, mp 170°.
THERAP CAT: Antihypertensive.

8389. Riluzole. *6-(Trifluoromethoxy)-2-benzothiazolamine;* 2-amino-6-(trifluoromethoxy)benzothiazole; PK-26124; RP-54274. $C_8H_5F_3N_2OS$; mol wt 234.20. C 41.03%, H 2.15%, F 24.34%, N 11.96%, O 6.83%, S 13.69%. Modulates glutamatergic transmission. Prepn: L. M. Yagupol'skii, *L. Z. Gandel'sman, Zh. Obshch. Khim.* **33**, 2301 (1963), *C.A.* **60**, 692a (1964). Prepd but not claimed: J. Mizoule, Eur. pat. Appl. 50,551; *idem*, U.S. pat. 4,370,338 (1982, 1983 both to Pharmindustrie). Pharmacology: J. Mizoule *et al.*, *Neuropharmacology* **24**, 767 (1985); F. Wahl *et al.*, *Eur. J. Pharmacol.* **230**, 209 (1993). Mechanism of action studies: M.-W. Debono *et al.*, *ibid.* **235**, 283; D. Martin *et al.*, *ibid.* **250**, 473. Use in treatment of motor nerve diseases: E. Louvel, Eur. pat. Appl. 558,861 (1993 to Rhône-Poulenc Rorer). Clinical study in amyotrophic lateral sclerosis: G. Bensimon *et al.*, *N. Engl. J. Med.* **330**, 585 (1994).



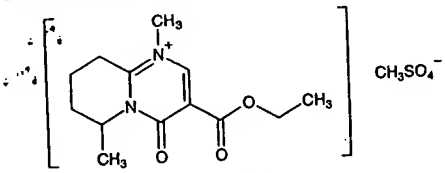
Crystals from ethanol/water (1:1), mp 119°. LD_{50} in mice (mg/kg): 46 i.p.; 67 orally (Mizoule).
THERAP CAT: Neuroprotective.

8390. Rimantadine. *α-Methyltricyclo[3.3.1.1^{3,7}]decane-1-methanamine; α-methyl-1-adamantanemethylamine;* remantadin(e). $C_{12}H_{21}N$; mol wt 179.31. C 80.38%, H 11.80%, N 7.81%. Deriv of adamantane, *q.v.* Prepn: Neth. pat. Appl. 6,408,505; W. W. Prichard, U.S. pat. 3,352,912 (1965, 1967 both to du Pont). Antiviral activity: A. Tsunoda *et al.*, *Antimicrob. Ag. Chemother.* **1965**, 553. Effects on influenza in mice: J. W. McGahen *et al.*, *Ann. N.Y. Acad. Sci.* **173**, 557 (1970). Mechanism of action study: A. Bukrinskaya *et al.*, *Arch. Virol.* **66**, 275 (1980); *eidem*, *J. Gen. Virol.* **60**, 49 (1982). Pharmacokinetics in humans: R. J. Wills *et al.*, *Antimicrob. Ag. Chemother.* **31**, 826 (1987). Clinical trial in prophylaxis of influenza A infection: R. Dolin *et al.*, *N. Engl. J. Med.* **307**, 580 (1982). Comparative toxicity of rimantadine and amantadine in healthy adults: F. G. Hayden *et al.*, *Antimicrob. Ag. Chemother.* **19**, 226 (1981). Controlled study of CNS effects: V. M. Millet *et al.*, *ibid.* **21**, 1 (1982). Review of studies in the USSR on exptl and clinical pharmacology: D. M. Zlydnikov *et al.*, *Rev. Infect. Dis.* **3**, 408-421 (1981).



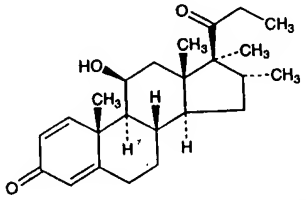
Hydrochloride, $C_{12}H_{21}N.HCl$, *EXP-126, Flumadine, Meradan(e), Roflual.* White crystals, mp 373-375° (sealed tube).
THERAP CAT: Antiviral.

8391. Rimazolium Metilsulfate. *3-(Ethoxycarbonyl)-6,7,8,9-tetrahydro-1,6-dimethyl-4-oxo-4H-pyrido[1,2-a]pyrimidinium methyl sulfate; 3-carboxy-6,7,8,9-tetrahydro-1,6-dimethyl-4-oxo-4H-pyrido[1,2-a]pyrimidinium methyl sulfate, ethyl ester;* 1,6-dimethyl-3-carbethoxy-4-oxo-6,7,8,9-tetrahydrohomopyrimidazole methyl sulfate; MZ-144; MZ-0780; Ro-11-780; Dolcuran; Probon; Probonal; Rimagina. $C_{14}H_{22}N_2O_7S$; mol wt 362.40. C 46.40%, H 6.12%, N 7.73%, O 30.90%, S 8.85%. Prepn: Z. Mészáros *et al.*, Hung. pat. Teljes 519 (1970 to Chinoin), *C.A.* **74**, 42374h (1971); *eidem, Arzneimittel-Forsch.* **22**, 815 (1972). Anti-inflammatory and analgesic effects in animals: K. Gyires *et al.*, *Drugs Exptl. Clin. Res.* **11**, 493 (1985). Clinical analgesic effect: H. Graber, *Int. J. Clin. Pharmacol. Ther. Toxicol.* **6**, 354 (1972); M. Haataja *et al.*, *Curr. Ther. Res.* **22**, 784 (1977). Series of articles on pharmacology, pharmacodynamics and toxicology: *Arzneimittel-Forsch.* **21**, 717-738 (1971). Toxicity data: J. Knoll *et al.*, *ibid.* 719.



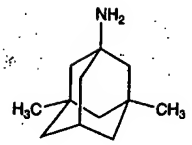
White crystals, mp 165-166°. uv max: 336, 258 nm (ε 3630, 27500). Readily sol in water. LD_{50} in rats (mg/kg): 220 i.v.; 720 i.p.; 790 s.c.; 1600 orally (Knoll).
THERAP CAT: Analgesic.

8392. Rimexolone. *(11β,16α,17β)-11-Hydroxy-16,17-dimethyl-17-(1-oxopropyl)androsta-1,4-dien-3-one;* 11β-hydroxy-16α,17α-dimethyl-17-propionylandrosta-1,4-dien-3-one; 11β-hydroxy-16α,17α,21-trimethylpregna-1,4-diene-3,20-dione; trimexolone; Org-6216; Rimexel; Vexol. $C_{24}H_{34}O_3$; mol wt 370.53. C 77.80%, H 9.25%, O 12.95%. Prepn: Neth. pat. Appl. 7,300,313; G. F. Woods *et al.*, U.S. pat. 3,947,478 (1973, 1976 both to Akzo); J. Cairns *et al.*, *J. Chem. Soc. Perkin Trans. I* **1981**, 2306. Pharmacology: P. K. Fox *et al.*, *Arzneimittel-Forsch.* **30**, 55 (1980). Clinical trial in rheumatoid arthritis: E. van Vliet-Daskalopoulou *et al.*, *Brit. J. Rheumatol.* **26**, 450 (1987). Clinical pharmacokinetics: G. Gevers *et al.*, *Clin. Rheumatol.* **13**, 103 (1994).



Crystals, mp 258-268°. $[\alpha]_D$ +100° (c = 0.92 in pyridine). uv max: 244 nm (ε 14600).
THERAP CAT: Anti-inflammatory (local).

8393. Rimiterol. *4-(Hydroxy-2-piperidinylmethyl)-1,2-benzenediol; erythro-α-(3,4-dihydroxyphenyl)-2-piperidinemethanol; erythro*-3,4-dihydroxyphenyl-2-piperidinylcarbinol. $C_{12}H_{17}NO_3$; mol wt 223.27. C 64.55%, H 7.67%, N

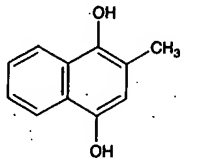


Oil, n_D^{25} 1.4941.

Hydrochloride, $C_{12}H_{21}N.HCl$, *Akatinol.* Cryst from alcohol/ether, mp 258° (Mills, Krumkalns); also reported as mp 290-295° (Gerzon).

THERAP CAT: Muscle relaxant (skeletal).

5873. Menadiol. *2-Methyl-1,4-naphthalenediol;* 2-methyl-1,4-naphthohydroquinone; 2-methyl-1,4-naphthoquinol; dihydrovitamin K_3. $C_{11}H_{10}O_2$; mol wt 174.20. C 75.84%, H 5.79%, O 18.37%. Synthetic naphthoquinol derivative having physiological properties of Vitamin K; *q.v.*; starting material for prepn of menaquinones, *q.v.* Prepn: K. Fries, W. Lohmann, *Ber.* **54**, 2912 (1921); D. W. MacCorquodale *et al., J. Biol. Chem.* **131**, 357 (1939); C. D. Snyder, H. Rapoport, *J. Am. Chem. Soc.* **96**, 8046 (1974). Crystal structure: J. Gaultier, C. Hauw, *Acta Crystallogr.* **25B**, 51 (1969). Bioactivity and tissue distribution: M. J. Thierry, J. W. Suttie, *J. Nutr.* **97**, 512 (1969).



White needles from dil alcohol, mp 168-170° (MacCorquodale); also reported as mp 181° (Gaultier, Hauw). Slightly sol in benzene, chloroform; easily sol in acetone, alcohol.

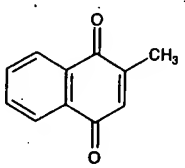
Diacetate, $C_{15}H_{14}O_4$, *1,4-diacetoxy-2-methylnaphthalene, acetomenaphthone, vitamin K_4, Kapilin, Prokayvit Oral, Vitavel K.* Prepn: Sah *et al., Ber.* **73**, 762 (1940); *Rec. Trav. Chim.* **59**, 461 (1940). Crystals, mp 112-114°. Practically insol in water. Slightly sol in cold alc; sol in 3.3 parts boiling alc, in acetic acid.

Dibutyrate, $C_{19}H_{22}O_4$, *Karanum.* Prepn: von Werder, Ger. pat. **734,220** (1943 to E. Merck). Crystals, mp ~53°. Practically insol in water. Sol in alcohol, benzene, oils and fats.

Sodium diphosphate, $C_{11}H_8Na_4O_8P_2$, *2-methyl-1,4-naphthalenediol diphosphoric acid ester tetrasodium salt, Kappadione, Synkavit, Synkayvite.* Prepn: Fieser, Fry, *J. Am. Chem. Soc.* **62**, 228 (1940). Prepd as the hexahydrate, white to pinkish powder. Salty taste. Very sol in water. Practically insol in methanol, ethanol, ether, acetone.

THERAP CAT: Vitamin (prothrombogenic).

5874. Menadione. *2-Methyl-1,4-naphthalenedione; 2-methyl-1,4-naphthoquinone;* menaphthone; Vitamin $K_{2(0)}$; Vitamin K_3; Kanone; Kappaxin; Kayklot; Kayquinone; Klottone; Kolklot; Thyloquinone. $C_{11}H_8O_2$; mol wt 172.18. C 76.73%, H 4.68%, O 18.58%. Synthetic naphthoquinone derivative having physiologic properties of vitamin K, *q.v.* Prepn: Fieser, *J. Biol. Chem.* **133**, 391 (1940). Toxicity study: Molitor, Robinson, *Proc. Soc. Exp. Biol. Med.* **43**, 725 (1940). Alkylated *in vivo* to the bioactive metabolite, menaquinone-4, *q.v.*: C. Martius, H. O. Esser, *Biochem. Z.* **331**, 1 (1958). Metabolism and tissue distribution: W. V. Taggart, J. T. Matschiner, *Biochemistry* **8**, 1141 (1969). Improved synthesis: W. Adam *et al., Angew. Chem. Int. Ed. Engl.* **33**, 2475 (1994).



Bright yellow crystals. Very faint acrid odor. mp 105-107°. Stable in air; dec by sunlight. Insol in water. One gram dissolves in about 60 ml alcohol, in 10 ml benzene, in 50 ml vegetable oils; moderately sol in chloroform and in carbon tetrachloride. Thé alcoholic soln is neutral to litmus. Solutions may be heated to 120° without dec. Destroyed by alkalies and reducing agents. *Keep protected from light.* LD_{50} orally in mice: ~0.5 g/kg (Molitor, Robinson).

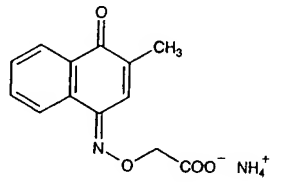
Sodium bisulfite, $C_{11}H_9NaO_5S$, *1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid sodium salt, Abor K, Hykinone, Izokappa, Klotogen, K-Thrombin.* Prepn: Moore, *J. Am. Chem. Soc.* **63**, 2049 (1941). Structure: Carmack *et al., ibid.* **72**, 844 (1950). Occurs as the trihydrate. White, hygroscopic crystals. Discolors and may turn purple under the influence of light. One gram dissolves in ~2 ml water. Slightly sol in alcohol. Almost insol in ether, benzene.

Dimethylpyrimidinol bisulfite, $C_{17}H_{18}N_2O_6S$, *Hetrazeen.* Prepn: J. B. Nanninga *et al.*, U.S. pat. **3,328,169** (1967 to Heterochemical). Efficacy in swine diets: R. W. Seerley *et al., J. Anim. Sci.* **42**, 599 (1976). Cryst powder, mp 215-217°. Soly in water ~1 g/100 ml. Slightly sol in alcohol. Insol in ether, benzene.

THERAP CAT: Vitamin (prothrombogenic).

THERAP CAT (VET): Vitamin (prothrombogenic); antidote to bishydroxycoumarin poisoning, including sweet clover poisoning.

5875. Menadoxime. *[[(3-Methyl-4-oxo-1(4H)-naphthalenylidene)amino]oxy]acetic acid ammonium salt; menadione carboxymethoxime ammonium salt;* menaphthone carboxymethoxime ammonium salt; carboxymethylmenadione monoxime ammonium salt; Kapilon injectable. $C_{13}H_{14}N_2O_4$; mol wt 262.27. C 59.54%, H 5.38%, N 10.68%, O 24.40%. Prepn: Holland, **Brit. pat. 621,934** (1949 to Glaxo).



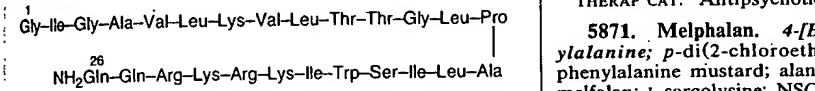
Crystals from alc. Sol in water. Aq solns are neutral. May be sterilized by autoclaving and stored in ampuls if protected from light. Shows high antihemorrhagic activity.

Free acid, $C_{13}H_{11}NO_4$, yellow platelets from alc, mp 162-163°. Forms water-sol salts.

THERAP CAT: Vitamin (prothrombogenic).

5876. Menaquinones. Vitamin K_2; 2-methyl-3-*all-trans*-polyprenyl-1,4-naphthoquinones. Group of prenylated napthoquinone derivatives having the physiological activity of vitamin K, *q.v.* Nomenclature is based on the number of isoprene residues comprising the side chain. Compds of varying chain length are produced by bacteria, particularly by normal intestinal flora, and may serve as a source of vitamin K for humans. Birds and animals are capable of alkylating menadione, *q.v.*, to produce menaquinone 4. Originally isolated from putrefied fish meal: R. W. McKee *et al., J. Biol. Chem.* **131**, 327 (1939). Identification of menaquinone 6: S. B. Binkley *et al., ibid.* **133**, 721 (1940). Isoln of menaquinone 7 from cultures of *Bacillus brevis:* M. Tishler, W. L. Sampson, *Proc. Soc. Exp. Biol. Med.* **68**, 136 (1948). Structures and syntheses of series of menaquinones: O. Isler *et al., Helv. Chim. Acta* **41**, 786 (1958). Review of isoln, props, synthesis: O. Isler, O. Wiss, *Vitam. Horm.* **17**, 53-90 (1959); H. Mayer, O. Isler, *Methods Enzymol.* **18C**, 469-547 (1971); of biosynthesis: D. R. Threlfall, *Vitam. Horm.* **29**, 153-200 (1971); R. Bentley, R. Meganathan, *Microbiol. Rev.* **46**, 241-280 (1982). Menaquinones with side chains of up to 15 repeating units have been described: T. Sakano *et al., Cehm. Pharm. Bull.* **34**, 4322 (1986). HPLC determn in bone: S. J. Hodges *et al., J. Bone Mineral Res.* **8**, 1005 (1993). Metabolism and distribution: H. H. W. Thijssen, M. J. Drittij-Reijnders, *Brit. J. Nutr.* **72**, 415 (1994).

367 (1954); Habermann, Reiz, *Biochem. Z.* **341**, 451 (1965). Melittin is the first polypeptide whose biological effects can be understood on the basis of its primary structure. Elucidation of structure and correlation with activity: E. Habermann, J. Jentsch, *Z. Physiol. Chem.* **348**, 37 (1967). Conformation studies: R. Bazzo *et al., Eur. J. Biochem.* **173**, 139 (1988). About 10% of the melittin is thought to be formylated at the *N*-terminus: Kreil, Kreil-Kiss, *Biochem. Biophys. Res. Commun.* **27**, 275 (1967). Isoln and structure of *N*-*formyl melittin*: Lübke *et al., Experientia* **27**, 765 (1971). Synthesis of melittin and related peptides: Lübke, Schröder, *Peptides*, H. C. Beyerman, A. van der Linde, W. M. van den Brink, Eds. (North-Holland Publishing Company, Amsterdam, 1967) pp 271-279; Dorman, Markley, *J. Med. Chem.* **14**, 5 (1970); Schröder *et al., Experientia* **27**, 764 (1971). Solid phase synthesis and purification: M. T. Tosteson *et al., Biochemistry* **26**, 6627 (1987). Review of biochemistry and pharmacology: Habermann, *Science* **177**, 314 (1972).



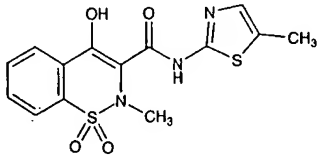
Cream white, water soluble powder. $[\alpha]_D^{21}$ −89.52° (c = 0.409).

THERAP CAT: Antirheumatic.

5868. Mellitic Acid. *Benzenehexacarboxylic acid;* mellic acid. $C_{12}H_6O_{12}$; mol wt 342.17. C 42.12%, H 1.77%, O 56.11%. $C_6(COOH)_6$. Preparation from carbonaceous material: M. Kiebler, U.S. pat. 2,461,740 (1949 to Carnegie Inst. of Tech.); Germain *et al., Bull. Soc. Chim. France* **1962**, 779; from tetrahalophthalic acid: Brusset, Uny, *ibid.* **1951**, 565; Juettner, U.S. pat. 3,067,246 (1962).

Crystals. mp 286-288° in sealed tube with decompn. Freely sol in water or alcohol; sol in boiling concd H_2SO_4 without decompn.

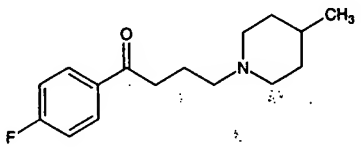
5869. Meloxicam. *4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide;* Metacam. $C_{14}H_{13}N_3O_4S_2$; mol wt 351.41. C 47.85%, H 3.73%, N 11.96%, O 18.21%, S 18.25%. Prepn: G. Trummlitz *et al.*, Ger. pat. 2,756,113 (1979 to Thomae); *eidem*, U.S. pat. 4,233,299 (1980 to Boehringer Ingelheim). Pharmacology: G. Engelhardt, G. Trummlitz, *Drugs Exp. Clin. Res.* **16**, 53 (1990). Tissue distribution in rats: U. Busch, G. Engelhardt, *ibid.* 49. Pharmacodynamics and pharmacokinetics in horses: P. Lees *et al., Brit. Vet. J.* **147**, 97 (1991). Physicochemical properties: R.-S. Tsai *et al., Helv. Chim. Acta* **76**, 842 (1993). Clinical efficacy in dogs: A. J. Henderson *et al., Prakt. Tierarzt.* **75**, 179 (1994).



Crystals from ethylene chloride, mp 254° (dec). pKa: 4.08 in water; 4.24 ± 0.01 in water/ethanol (1:1); 4.63 ± 0.03 in water/ethanol (1:4). Log P_{oct} 3.02. LD_{50} orally in mice: 470 mg/kg (Trummlitz, 1980).

THERAP CAT (VET): Anti-inflammatory.

5870. Melperone. *1-(4-Fluorophenyl)-4-(4-methyl-1-piperidinyl)-1-butanone; 4'-fluoro-4-(4-methylpiperidino)-butyrophenone;* γ-(4-methylpiperidino)-*p*-fluorobutyrophenone; methylperone; flubuperone. $C_{16}H_{22}FNO$; mol wt 263.36. C 72.97%, H 8.42%, F 7.21%, N 5.32%, O 6.08%. Neuroleptic agent related structurally to haloperidol, *q.v.* Prepn: Belg. pat. 651,144; S. E. H. Hernestam *et al.*, U.S. pat. 3,816,433 (1964, 1974 both to Ferrosan). Distribution of ^{14}C melperone: N. Einer-Jensen, E. Hansson, *Acta Pharmacol. Toxicol.* **23**, 65 (1965). Pharmacological and toxicological studies: J. A. Christensen *et al., ibid.* 109; R. Heywood, A. K. Palmer, *Farmaco Ed. Prat.* **29**, 586 (1974). Dopamine-receptor binding in relation to clinical effect: I. Creese *et al., Science* **192**, 481 (1976). Sedative and sleep-inducing properties: R. Kretzschmer *et al., Arzneimittel-Forsch.* **26**, 1073 (1976). Clinical studies in anxiety: W. J. Poeldinger, *Therapiewoche* **30**, 4862 (1980); L. F. Fabre, M. J. Napoliello, *Curr. Ther. Res.* **30**, 427 (1981).

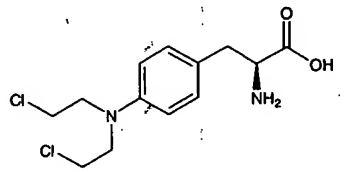


Liquid, $bp_{0.1}$ 120-125°.

Hydrochloride, $C_{16}H_{22}FNO.HCl$, *FG-5111, Buronil, Eunerpan.* Crystals, mp 209-211°. LD_{50} in rats, mice (mg/kg): 330, 230 orally; 40, 35 i.v. (Christensen).

THERAP CAT: Antipsychotic.

5871. Melphalan. *4-[Bis(2-chloroethyl)amino]-L-phenylalanine; p*-di(2-chloroethyl)amino-L-phenylalanine; L-phenylalanine mustard; alanine nitrogen mustard; L-PAM; melfalan; L-sarcolysine; NSC-8806; CB-3025; Alkeran; Sarcoclorin. $C_{13}H_{18}Cl_2N_2O_2$; mol wt 305.20. C 51.16%, H 5.94%, Cl 23.23%, N 9.18%, O 10.48%. Syntheses: Bergel, Stock, *J. Chem. Soc.* **1954**, 2409; **1955**, 1223; *eidem*, U.S. pats. 3,032,584; 3,032,585 (both 1962 to NRDC); Larionov, *Lancet* **2**, 169 (1955). Toxicity: W. C. J. Ross, *Biochem. Pharmacol.* **13**, 969 (1964). Neurotoxicity study: M. G. Donelli *et al., J. Pharm. Pharmacol.* **18**, 760 (1966). Mutation study: J. McCann *et al., Proc. Nat. Acad. Sci. USA* **72**, 5135 (1975). Biliary excretion in rats: K. H. Byington *et al., Biochem. Pharmacol.* **29**, 2518 (1980). Review of carcinogenicity studies: *IARC Monographs* **9**, 167-180 (1975). *Review:* R. L. Furner, R. K. Brown, *Cancer Treat. Rep.* **64**, 559-574 (1980).



Needles from methanol (monosolvate), mp 182-183° (dec). $[\alpha]_D^{25}$ +7.5° (c = 1.33 in 1.0*N* HCl); $[\alpha]_D^{22}$ −31.5° (c = 0.67 in methanol). Soluble in ethanol, propylene glycol. Practically insol in water. LD_{50} i.p. in rats: 14.7 μmol/kg (Ross).

D-Form, *D-sarcolysine, medphalan, CB-3026, NSC-35051.* Needles from methanol (monosolvate), mp 181.5-182° (dec). $[\alpha]_D^{21}$ −7.5° (c = 1.26 in 1.0*N* HCl).

DL-Form, *merphalan, sarcolysine.* Tiny needles from methanol, mp 180-181°.

Note: This substance has been listed as a known carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 60.

THERAP CAT: Antineoplastic.

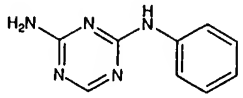
5872. Memantine. *3,5-Dimethyltricyclo[3.3.1.1^{3,7}]decan-1-amine; 3,5-dimethyl-1-adamantanamine;* 1-amino-3,5-dimethyladamantane; DMAA; D-145. $C_{12}H_{21}N$; mol wt 179.31. C 80.38%, H 11.80%, N 7.81%. Deriv of adamantine, *q.v.*, with anti-parkinson activity. Prepn of the hydrochloride: K. Gerzon *et al., J. Med. Chem.* **6**, 760 (1963); of the free base and hydrochloride: J. Mills, E. Krumkalns, U.S. pat. 3,391,142 (1968 to Lilly). GC and mass spec studies of memantine metabolites: W. Wesemann *et al., Arzneimittel-Forsch.* **27**, 1471 (1977). Effects in parkinsonian patients: P.-A. Fischer *et al., ibid.* 1487. Series of articles on distribution, effects on neurobiological processes, clinical studies in control of micturition and limb muscle mobility: *ibid.* **32**, 1236-1276 (1982). Clinical studies as antispasmodic agent: H. Rohde, *Fortschr. Med.* **100**, 2023 (1982). Pharmacodynamics and pharmacokinetics: W. Wesemann *et al., Arzneimittel-Forsch.* **33**, 1122 (1983).

β-Amanitin, $C_{39}H_{53}N_9O_{15}S$. Needles from methanol, mp 300°. uv max: 302 nm. Sol in water, methanol, ethanol, aqueous butanol. LD_{50} i.p. in albino mice: 0.4 mg/kg (Wieland, Wieland).

Caution: Highly toxic. Following a characteristic asymptomatic period of 6-15 hrs, potential symptoms of intoxication due to ingestion include violent gastroenteritis; fever, tachycardia, hyperglycemia, dehydration, electrolyte imbalance; liver dysfunction and necrosis; renal failure; may be fatal. *See Clinical Toxicology of Commercial Products,* R. E. Gosselin *et al.,* Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section II, p 246; M. J. Ellenhorn, D. G. Barceloux, *Medical Toxicology: Diagnosis and Treatment of Human Poisoning* (Elsevier, New York, 1988) pp 1331-1338.

USE: As a tool in molecular biology.

388. Amanozine. *N-Phenyl-1,3,5-triazine-2,4-diamine; 2-amino-4-anilino-s-triazine;* 4-amino-2-anilino-1,3,5-triazine; 2-amino-6-anilino-*s*-triazine; *N*-phenylformoguanamine; W-1191-2; Urofort. $C_9H_9N_5$; mol wt 187.20. C 57.74%, H 4.85%, N 37.41%. Prepd by the action of formic acid on phenylbiguanide: Papini, Folena, *Gazz. Chim. Ital.* 80, 837 (1950); **Austrian** pat. **168,063** (1951 to Gedeon Richter), *C.A.* **47**, 8097h (1953); from phenylbiguanide and ethyl formate in methanol in 67% yield: Overberger, Shapiro, *J. Am. Chem. Soc.* **76**, 93 (1954).

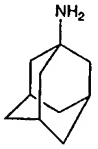


Crystals from dioxane or 50% ethanol, mp 235-236°. Precipitated by alkalies.

Hydrochloride, $C_9H_9N_5.HCl$, long needles, dec 258-260°.

THERAP CAT: Diuretic.

389. Amantadine. *Tricyclo[3.3.1.1^{3,7}]decan-1-amine; 1-adamantanamine;* 1-aminoadamantane; 1-aminodiamantane (obsolete); 1-aminotricyclo[3.3.1.1^{3,7}]decane. $C_{10}H_{17}N$; mol wt 151.25. C 79.41%, H 11.33%, N 9.26%. Synthesis (two different routes): Stetter *et al., Ber.* **93**, 226 (1960); *cf. Angew. Chem.* **71**, 429-430 (1959); from adamantyl chloride: Gerzon *et al., J. Med. Chem.* **6**, 760 (1963). Prepn: **Brit.** pat. **925,728** corresp to **U.S.** pat. **3,152,180** (1963, 1964 both to Studiengesellschaft Kohle); **Belg.** pat. **646,581** (1964 to Du Pont), *C.A.* **63**, 14726h (1965). Pharmacology and toxicology: Vernier *et al., Toxicol. Appl. Pharmacol.* **15**, 642 (1969). Metabolism: Bleidner *et al., J. Pharmacol. Exp. Ther.* **150**, 484 (1965). Clinical trial in prophylaxis of influenza A infection: R. Dolin *et al., N. Engl. J. Med.* **307**, 580 (1982). *See also* Adamantane, Rimantadine. Comprehensive description: J. Kirschbaum, *Anal. Profiles Drug Subs.* **12**, 1-36 (1983).



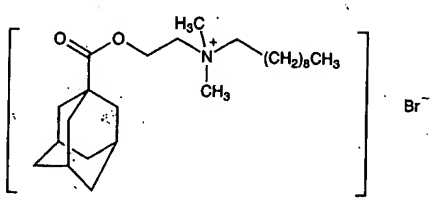
Hexakistetrahedral crystals by sublimation, mp 160-190° (closed tube). Also reported as mp 180-192°. Sparingly sol in water.

Hydrochloride, $C_{10}H_{17}N.HCl$, *EXP-105-1, NSC-83653, Amazolon, Mantadix, Mantadan, Mantadine, Midantan, Mydantane, Symmetrel, Virofral.* Crystals from abs ethanol + anhydr ether, dec 360°. Sol in water (at least 1:20), alc. Practically insol in ether. LD_{50} orally in mice, rats: 700, 1275 mg/kg (Vernier).

Sulfate, *PK-Merz, Trivaline.*

THERAP CAT: Antiviral (Influenza A); antiparkinsonian; treatment of drug-induced extrapyramidal reactions.

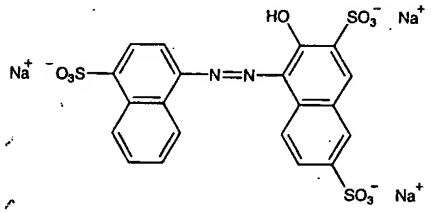
390. Amantanium Bromide. *N,N-Dimethyl-N-[2-[(tricyclo[3.3.1.1^{3,7}]dec-1-ylcarbonyl)oxy]ethyl]-1-decanaminium bromide;* 2-(1′-adamantanecarbonyloxy)ethyldimethyldecylammonium bromide; decyl(2-hydroxyethyl)dimethylammonium bromide 1-adamantanecarboxylate; Amantol. $C_{25}H_{46}BrNO_2$; mol wt 472.55. C 63.54%, H 9.81%, Br 16.91%, N 2.96%, O 6.77%. Prepn: R. A. Bauman, **U.S.** pat. **3,928,411** (1975 to Colgate-Palmolive); and activity: L. Rovati *et al.,* **U.S.** pat. **4,288,609** (1981 to Rotta).



Crystals, mp 182-184°. LD_{50} orally in mice: 910 mg/kg (Rovati).

THERAP CAT: Antiseptic.

391. Amaranth (Dye). *3-Hydroxy-4-[(4-sulfo-1-naphthalenyl)azo]-2,7-naphthalenedisulfonic acid trisodium salt; C.I. Acid Red 27;* C.I. 16185; FD & C Red No. 2; Red no. 2; trisodium salt of 1-(4-sulfo-1-naphthylazo)-2-naphthol-3,6-disulfonic acid. $C_{20}H_{11}N_2Na_3O_{10}S_3$; mol wt 604.48. C 39.74%, H 1.83%, N 4.63%, Na 11.41%, O 26.47%, S 15.91%. Prepd by coupling diazotized α-naphthylamine-4-sulfonic acid with β-naphthol-3,6-disulfonic acid: Knecht, *J. Soc. Dyers Colour.* **2**, 24 (1886); Farbw. Hoechst, **Ger.** pat. **3229; Brit.** pat. **1715; BASF, Ger.** pat. **5411; U.S.** pat. **204,799.** Metabolism: J. L. Radomski, T. J. Mellinger, *J. Pharmacol. Exp. Ther.* **136**, 259 (1962). *See also Colour Index* **vol. 4** (3rd ed., 1971) p 4093.



Dark, reddish-brown powder. Absorption max (water): 522.5 nm. One gram dissolves in about 15 ml water. Also reported as 7.20 g/100 ml H_2O at 26°. Very slightly soluble in alcohol. The aq soln is vivid red (1 cm layer). Discharge white by hydrosulfite on wool and silk. HCl does not change the color intensity of the soln, NaOH increases it. The aq soln is stable toward light.

Caution: Banned by the FDA in 1976 for use in foods, drugs and cosmetics.

USE: Dyeing wool and silk bright bluish-red from an acid bath. As indicator in hydrazine titrations. In color photography.

392. Amaranth (Plant). Genus of the *Amaranthaceae* L. family which contains approx 60 species having worldwide distribution. Many species are considered weeds but *Amaranthus caudatus* L. (*love-lies-bleeding*), *A. hybridus* variety *hypochondriacus* L. (*prince's feather*), *A. tricolor* have been cultivated as ornamentals. *A. retroflexus* L. and some of the other weedy species are known as *pigweed, redroot* and *water hemp. A. spinosus* L. has been used in the treatment of gonorrhea: W. H. Brown, *Useful Plants of the Philippines* **1** (Philippines Dept. Agr. and Natl. Resources, Manila, 1951) pp 510-515; as a poultice in the treatment of inflammation, bruises and eczema: T. H. P. de Tavera, *The Medicinal Plants of the Philippines* (P. Blakiston's Son, Philadelphia, 1901) pp 200-202. Most species are hardy, herbaceous and fast-growing cereal-like plants. Leaves and grain are used for food in parts of South America, Africa and Asia. Plants are high in protein; the amino acid composition is complementary to that of wheat. The grain was a basic food in pre-Columbian South and Central America and was important in Aztec ritual. Grain amaranths (*A. hypochondriacus, A. cruentas, A. caudatus*) produce large seedheads containing many edible seeds. The seed can be

(B) Preparation of Form II of Memantine hydrochloride:

Example 1:

5.0 gm Memantine hydrochloride is dissolved in 40 ml water at 80-85^{0}C and gradually cooled to room temperature in 1hour time and further maintained at room temperature for 1 hour. The material is filtered and washed with 10 ml of DM water and dried at 40-50^{0}C to yield crystal form II of memantine hydrochloride.

Example 2:

5.0 gm Memantine hydrochloride is dissolved in 30 ml of water + ethanol mixture (5% water in ethanol) at 50^{0}C and gradually cooled to room temperature in 1hour time and further maintained at room temperature for 3 hours and cooled to 0-5^{0}C. The solvent is distilled under vacuum and degassed to yield crystal form II of memantine hydrochloride.

Example 3:

To memantine hydrochloride is added acetone at room temperature. Stir for 10 min at 25-35^{0}C. Distill out the acetone and degas. To the crude product so generated is added acetone and the contents of the flask are heated at 40-45^{0}C and stirred for 1 hour at that temperature. Cool the contents gradually to 0-5^{0}C over the period of 2-3 hours. Stir the contents for 1 hour at 0-5^{0}C. Filter the product and wash with chilled acetone.

Crystal Form II exhibits x-ray powder diffraction pattern as represented in fig. 2.
Physical properties of Form II are tabulated in Table I

A comparison of the physical properties of Form I and Form II is given in Table I and stability study data for form II after storing under ambient conditions for 330 days is given in Table II.